

**IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK**

ANNIE TUMMINO, *et al.*,

Plaintiffs,

V.

MARGARET HAMBURG, Commissioner
of Food and Drugs, *et al.*,

Defendants.

Civil Action No. 12-CV-763

(Korman, J.)

(Pohorelsky, M.J.)

**MEMORANDUM IN SUPPORT OF
DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT**

Plaintiffs' APA claim hinges on the notion that it is FDA policy to extrapolate data from adults to pediatric populations. It unquestionably is not. As Defendants have explained, the question whether extrapolation is appropriate is a matter of scientific judgment that depends on the data and circumstances presented in each particular application. *See* Defs.' Opp'n to Pls.' Mot. for Summ. J. 35-36 (citing 21 C.F.R. § 314.105(c)). Plaintiffs' assertion that extrapolation is routine is both legally and factually incorrect.

To begin, Plaintiffs are wrong to suggest that the Pediatric Research Equity Act of 2003 (“PREA”), Pub. L. No. 108-155, 117 Stat. 1936 (2003), codified a general policy of extrapolation from adults to pediatric populations. Pls.’ Mem. 4-5 & n.3. In fact, that Act simply states that FDA “may” extrapolate under certain circumstances — not that it must. And that Act endorses extrapolation from adult studies only to support pediatric effectiveness — not safety or dosing.

PREA requires the sponsor of a relevant NDA or SNDA to submit with their application adequate information to (1) “assess the *safety and effectiveness* of the drug . . . for the claimed indications in all relevant pediatric subpopulations” and (2) “to support dosing and administration for each pediatric subpopulation for which the drug . . . is *safe and effective*.” 21 U.S.C. 355c(a)(2)(A) (emphasis added). It then states that “if course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary *may* conclude that pediatric *effectiveness* can be extrapolated from adequate and well-controlled studies in adults.” 21 U.S.C. 355c(a)(2)(B)(i) (emphasis added). The statute is silent on extrapolation for pediatric safety or dosing from adult studies. *See id.* Accordingly, where PREA applies, it is FDA’s practice to permit extrapolation from adult studies to pediatric populations to support effectiveness, but not safety or dosing. *See generally* FDA, Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act 5-6 (2005), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079756.pdf> (all Internet addresses last visited July 19, 2012); *see also* 21 C.F.R. § 201.80(f)(9)(iv) (describing, under OTC labeling regulations, approval of a drug for pediatric use based in part on “extrapolation from the adult efficacy data to pediatric patients”); Opening Remarks: Remicade (infliximab) GI Advisory Committee Meeting at 7, 9 (noting that dosing and safety cannot be extrapolated from adult studies and presenting a “Pediatric Extrapolation Decision Tree” used by CDER to determine whether extrapolation is appropriate), available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf>.

Moreover, even FDA’s extrapolation from adult studies to support pediatric effectiveness

cannot be considered routine. In a 2011 article, FDA scientists reviewed the use of extrapolation in 166 drug products submitted for pediatric approval between 1998 and 2008. The authors concluded that FDA did not extrapolate efficacy data for 29 products (17.5%), partially extrapolated for 113 products (68%), and fully extrapolated for 24 products (14.5%). Julia Dunne et al., *Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs*, 128 *Pediatrics* e1242, e1245 at tbl. 1 (Nov. 1, 2011) (annexed as Ex. A).

Thus, it is by no means unusual for FDA to decline to extrapolate from adults to pediatric populations. For example, when a prescription drug is ready for approval for use in adults but pediatric studies have not been completed, rather than extrapolate, FDA may approve the application for adults while requiring the sponsor to submit additional post-marketing studies in pediatric populations. *See* 21 U.S.C. § 355c(a)(3)(A)(i)(I); *see, e.g.*, FDA, Approval Letter, Embeda, NDA 22-321 (Aug. 13, 2009) (requiring post-marketing studies for ages 2 to 17), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022321s000ltr.pdf; FDA, Approval Letter, BYDUREON, NDA 22-200 (Jan. 27, 2012) (requiring post-marketing studies for ages 10 to 17 years), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022200s000ltr.pdf; FDA, Approval Letter, Oleptro, NDA 22-411 (Feb. 2, 2012) (requiring post-marketing studies for ages 7 to 17 years), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022411s000ltr.pdf; FDA, Approval Letter, RECTIV, NDA 21-359 (June 21, 2011) (requiring post-marketing studies for ages 1 month to 16 years), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021359s000ltr.pdf; *see also* FDA, Postmarket Requirements and Commitments Database, *available at* <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm> (searchable database for

post-marketing studies required under PREA).

In such cases, drug sponsors are required to submit an annual report to FDA detailing progress towards completing the required post-marketing studies, *see* 21 U.S.C. § 355c (a)(3)(B)(i)(I); 21 C.F.R. § 314.81, and the product labeling must indicate that the drug has not been found safe and effective for the relevant pediatric age group, *see* 21 C.F.R. § 201.57(c)(9)(iv)(E)-(F); *see also* Embeda Label at 11 (Aug. 13, 2009) (“The safety and efficacy of EMBEDA in patients less than 18 years of age have not been established.”), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022321s000lbl.pdf; BYDUREON Label at 14 (Jan. 27, 2012) (“Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.”), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000bledt.pdf; Oleptro Label at 12 (Feb. 2, 2012) (“Safety and effectiveness in the pediatric population have not been established Oleptro should not be used in children or adolescents.”), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022411lbl.pdf; RECTIV Label at 6 (Jun. 21, 2011) (“The safety and effectiveness of RECTIV in pediatric patients under 18 years of age have not been established.”), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021359s000lbl.pdf.

In addition, drug sponsors routinely submit pediatric studies to support pediatric labeling for indications approved for adults, which would not be necessary if FDA could always reliably extrapolate from the studies supporting adult use. *See generally* FDA, Pediatric Study Characteristics, *available at* <http://www.accessdata.fda.gov/scripts/SDA/sdNavigation.cfm?filter=&sortColumn=1d&sd=fdaaadescriptorssortablewebdatabase&page=1> (table “summa-

riz[ing] pediatric studies that led to FDAAA pediatric labeling changes pursuant to the Best Pharmaceuticals for Children Act, and the Pediatric Research Equity Act”).

This is equally true for OTC approvals of drugs containing the same active ingredient as an Rx product. For example, Prilosec OTC was approved for frequent heartburn in 2003 for adults 18 and older. It was not approved for use by those under 18. An FDA review noted:

[t]here are 2% of total prescriptions in the 11 to 20y old age group and children have — in general — not been included in clinical trials; [Prilosec] is not approved for prescription use in adolescents (patients under 18y of age). There were only 100 OTC study subjects under age 18 (17% of whom exceeded the 10-day limit) and a total of 39 cases in SafeTNet. From this information, the Medical Officer concluded that safety in adolescents has not been established because: a) age-related responses have not been studied; and b) age-related toxicities cannot be ruled out.

NDA 21-229, Medical Team Review at 14 (Oct. 31, 2000), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-229_Prilosec_admindocs.pdf (pdf at 359). Similarly,

Alli was approved OTC for weight loss in 2007 only for adults 18 and older. FDA’s review concluded:

Treatment of obesity with the intent of weight loss in 12 to 17 year olds is complicated by the factor that this age group includes individuals that may still be in an active growth phase with continued bone and other organ, maturation and where nutritional requirements are different from those of adults. Therefore, the balance between active weight loss, while still continuing to have adequate nutritional requirements, would best be achieved in my judgment with active health care provider interaction. As such, I do not feel that this age group should be included in an over-the-counter label.

NDA 21-887, Office Director’s Decisional Memorandum at 3-4 (Feb. 6, 2007), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P1.pdf (pdf pages 8-9); *see also id.* at 4 (noting the availability of some “studies to inform the use of [Prilosec] in this age range, albeit for the prescription dose in a medically supervised setting”).

Thus, Plaintiffs fail to demonstrate any policy that requires extrapolation from adult

studies to pediatric populations in all cases. Indeed, both PREA and FDA practice demonstrate otherwise. As Defendants have explained, FDA's conclusion that extrapolation is appropriate is matter of scientific judgment that proceeds on a case-by-case basis. Here, FDA specifically explained why it determined that extrapolation was inappropriate. *See* Defs.' Opp'n to Pls.' Mot. for Summ. J. 35-37. That decision fell well within the range of reasonable scientific judgment, as even its sharpest critics have conceded. *See* Defs.' Resp. to Order to Show Cause 33-35. The APA requires nothing more.

CONCLUSION

For the foregoing reasons, in addition to those set forth in Defendants' response to the Court's show cause order [Case No. 12-763, Doc. No. 23] and Defendants' opposition to Plaintiffs' motion for a preliminary injunction and for summary judgment [Case No. 12-763, Doc. No. 37], the Court should grant Defendants' cross-motion for summary judgment and enter judgment in favor of Defendants on Count I of the Second Amended Supplemental Complaint.

Dated: July 20, 2012

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CERTIFICATE OF SERVICE

I hereby certify that on July 20, 2012, the foregoing document was filed with the Clerk of Court via the CM/ECF system, causing it to be served on Plaintiffs' counsel of record.

/s/ Eric B. Beckenhauer
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